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Research Article

The Stokes Number Approach to Support Scale-Up and Technology Transfer of a Mixing Process

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Abstract. Transferring processes between different scales and types of mixers is a common operation in industry. Challenges within this operation include the existence of considerable differences in blending conditions between mixer scales and types. Obtaining the correct blending conditions is crucial for the ability to break up agglomerates in order to achieve the desired blend uniformity. Agglomerate break up is often an abrasion process. In this study, the abrasion rate potential of agglomerates is described by the Stokes abrasion (St_{Abr}) number of the system. The St_{Abr} number equals the ratio between the kinetic energy density of the moving powder bed and the work of fracture of the agglomerate. In this study, the St_{Abr} approach demonstrates to be a useful tool to predict the abrasion of agglomerates during blending when technology is transferred between mixer scales/types. Applying the St_{Abr} approach revealed a transition point between parameters that determined agglomerate abrasion. This study gave evidence that (1) below this transition point, agglomerate abrasion is determined by a combination of impeller effects and by the kinetic energy density of the powder blend, whereas (2) above this transition point, agglomerate abrasion is mainly determined by the kinetic energy density of the powder blend.

KEY WORDS: dry mixing; scale-up; stokes number.

INTRODUCTION

One of the challenges during scale-up and technology transfer of a mixing process is that there usually are considerable differences in blending conditions between different mixer scales and types (1). Finding the blending conditions that lead to the desired blend uniformity is not a trivial operation (2,3). For this reason fill volume, impeller rotational speeds and blender geometry are preferably kept constant as much as possible during such a technology transfer (4,5). In practice this is not always possible. Moreover, such an approach does not necessarily mean that the blend conditions are always similar (6). Still, obtaining the correct blend conditions is crucial because only this safeguards formation of a sufficiently uniform blend. A specific, but frequently occurring case is a blend that contains cohesive components that tend to form agglomerates. Removal of these agglomerates and prevention

of the formation of new agglomerates is often the critical step in the assessment of the uniform blend (7,8).

Removal of agglomerates in a dry mixing system predominantly occurs via abrasion (8,9). The abrasion process is typically characterized by a high frequency of impacts by filler particles on the surfaces of the agglomerates. Mechanical properties of the agglomerates and product and process-related parameters like filler particle size and the rotational rate of the impeller were found to affect the size reduction rate of the agglomerates (8). It appeared to be possible to describe the abrasion process via definition of a Stokes number, the Stokes abrasion number (St_{Abr}). This number is the ratio of the kinetic energy density of the powder bed to the work of fracture of the agglomerate (9). Results so far showed that it is possible to predict effects of filler particle size and impeller rotation rate on abrasion rate with reasonable accuracy. The purpose of this study is to check the validity of the St_{Abr} approach and apply it to technology transfer situations where mixers of the same working mechanisms, but different production scales and different geometries are applied. Additionally, this paper identifies limits of applicability of the St_{Abr} approach.

EXPERIMENTAL

Materials

The materials used were microcrystalline cellulose (Avicel PH-101, FMC, Philadelphia, USA) and α -lactose monohydrate

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(Pharmatose® 100M from DMV Fonterra Excipients, Goch, Germany, with a bulk density of 750 kg/m³).

Methods

Model Agglomerates (Brittle Calibrated Test Particles)

The model agglomerates or spherical brittle calibrated test particles (bCTPs) were prepared as described before by Willemsz *et al.* (8). The porosities of all bCTPs produced were measured from the diameters and the weights of the bCTPs. The true density of the MCC was determined using a pycnometer (AccuPyc 1330, Micromeritics, Norcross, U.S.A.) using nitrogen as test gas and was found to be 1,600 kg/m³. The mechanical properties of the bCTPs have been described in Willemsz *et al.* (9).

Blending Tests

The blending experiments reported in this study were performed using convective mixers with bowl volumes of 25 l (Fukae Powtec model FS-GS-25J, Japan, bottom-driven impeller) and 50 l (Glatt model VG50, Germany equipped with a top-driven impeller). The chopper was never installed. Table I lists the parameters that were varied. A test was started by adding selected test particles to a powder sample of lactose 100 M. This mixture was placed in the blender. After a given blending time, the blend was sieved over a 500-μm sieve to collect the test particles. The weights and dimensions of the bCTPs were determined as a function of blending time as mentioned in the previous communication (8).

The Froude number (*Fr*) was calculated as follows:

$$Fr = \frac{N^2 D}{g} \quad (1)$$

With *N* the impeller rotational rate, *D* bowl diameter, and *g* is the acceleration of gravity.

Powder Surface Velocimetry

To collect data for powder surface velocimetry analysis, a plexiglass lid was placed on the 25-L granulator. The powder surface velocimetry data from the 50-L high-shear mixer were collected by recording through the watch glass of the apparatus.

Table I. Geometry of the High Shear Mixers and Experimental Set-Up for the blending Tests

	Mixer type	
	Fukae (25 L)	Glatt (50 L)
Geometry:		
Impeller type	Bottom driven	Bottom driven
Bowl Diameter (<i>D</i>) (m)	0.41	0.49
Impeller radius (m)	0.204	0.240
Impeller height (<i>h</i> _{impeller}) (m)	0.014	0.020
Experimental set-up:		
Relative fill volumes (<i>φ</i>) (%)	8, 16, 27, 37	16, 27, 37
Impeller rotational rates (<i>N</i>) (rpm)	100, 200, 300	85, 169, 254
Froude numbers (<i>Fr</i>) (–)	0.12, 0.46, 1.04	0.12, 0.46, 1.04

The powder flow was recorded using a high-speed video camera (Casio-EX-F1, Casio computer co., LTD, Tokyo, Japan) operating at a speed of 600 frames per second. The data were analyzed according to Willemsz *et al.* (10). The camera was placed perpendicular to the bowl and such that about 50% of the total powder surface was visible for the 25-L high-shear mixer and 25% of the surface in the 50-L high-shear mixer.

Statistical Analyses

The outlier diagnostics, standard deviation (SD) and 95% confidence interval calculations described in this paper were performed using SAS V9.1 software (SAS institute Inc., North Carolina, USA).

RESULTS AND DISCUSSION

Abrasion Rate Constant (ξ_m) Measurements in the 25- and 50-L High Shear-Mixer

In this study, two vertical axis high-shear mixers of different geometries (as described in Table II) were used to assess how the abrasion rate constants (ξ_m) of brittle agglomerates scale with process variables in high-shear mixers. The bCTPs mass reduction (*M*_{rel}) over time was determined. It obeys apparent first order kinetics, with mass reduction rate constant as described by Willemsz *et al.* (8):

$$M_{rel} = \frac{M(t)}{M_0} = e^{-\xi_m * t} \quad (2)$$

with *M*(*t*) as the mass after blending time *t* and *M*₀ as the initial mass.

The purpose of the current experiments was to investigate the effects of abrasion rate constants of agglomerates with different porosities when process variables are varied. The results are depicted in Fig. 1.

Figure 1 shows that the abrasion rate constants (ξ_m) of the agglomerates in the 50-L mixer are always lower than those obtained in the 25-L mixer when Froude numbers are identical. Abrasion rates increase with Froude number but decrease with increasing fill levels. These results are in line with findings discussed in previous papers (*e.g.* [8, 11–13]).

It is reasonable to assume that a reduction in fill volume implies that the contribution of the impeller to the total rate of agglomerate abrasion will increase. To visualize this effect additional tests have been performed where the powder just covers the impeller. This corresponds with a relative fill level of 8% in the 25-L mixer. Figure 2 shows the abrasion rates (ξ_m) of the bCTPs at different fill levels for two different *Fr*

Table II. Fit Parameters of Mechanical Properties Using $X = X_{0.55} \cdot e^{-k \cdot (\varepsilon - 0.55)}$ with $X = Y$ or $X = \sigma_c$ and $X_{0.55} = \sigma_c$ or Y at $\varepsilon = 0.55$ (The Data Indicate the Average ± 95% Confidence Interval)

Parameter	<i>X</i> =	<i>X</i> _{0.55}	<i>k</i>	<i>R</i> ²
Modulus (MPa)	<i>Y</i>	46.7 ± 6.0	16.9 ± 1.7	0.72
Fracture stress (MPa)	σ_c	1.1 ± 0.1	17.9 ± 1.4	0.80

An offset in ε of 0.55 has been introduced to reduce the extrapolation, because there are no data points in the ε range between 0 and 0.55

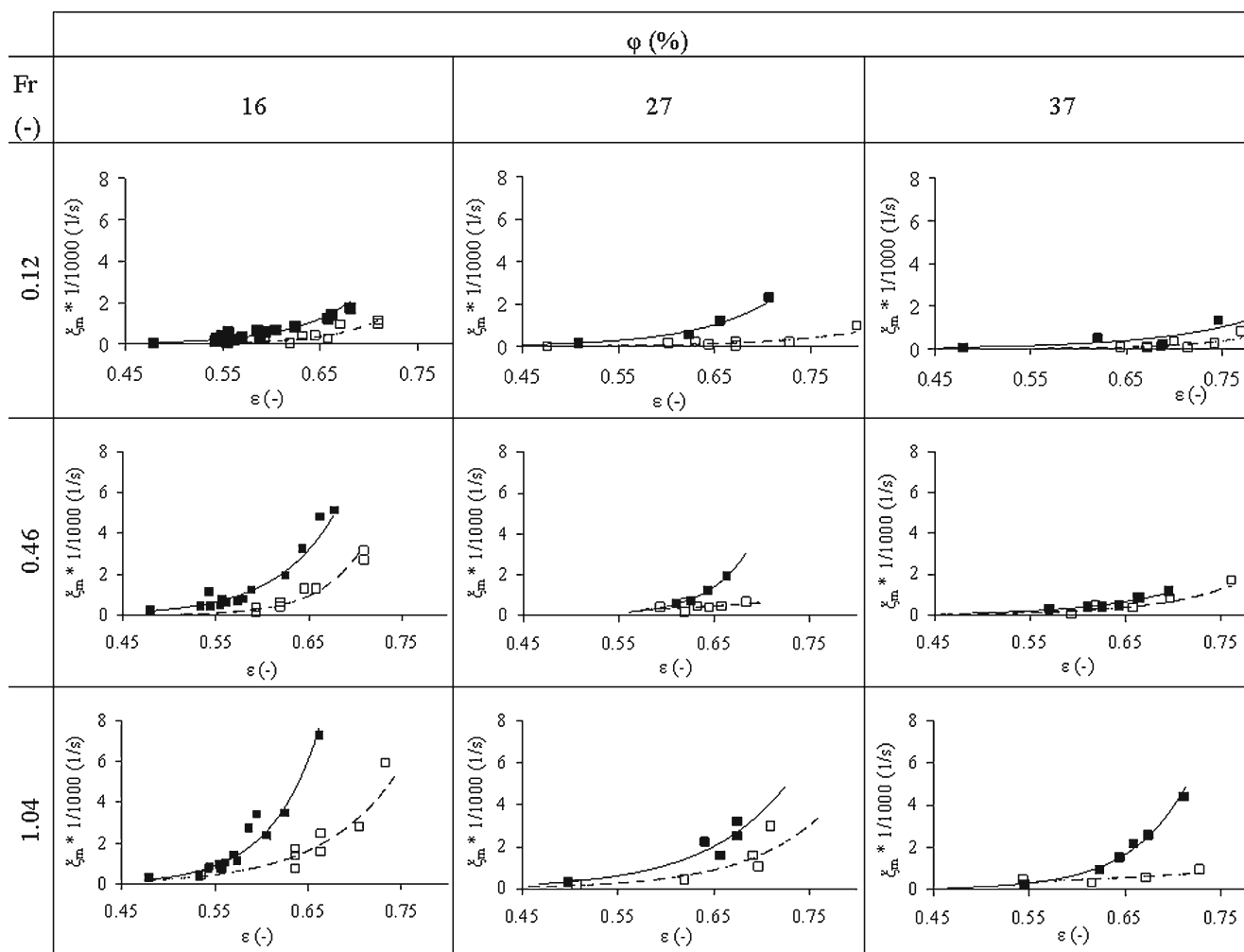


Fig. 1. The effect of process settings on the mass based abrasion rate constant for the 25-L (black square) and 50-L (white square) high-shear mixers. Fr represents the Froude number, ϕ the degree of fill of the equipment, ξ_m the abrasion rate constant and ε the porosity of the test particles (bCTPs)

numbers. Figure 2 clearly shows a considerable additional effect of the impeller at low fill levels on the abrasion rates of the particles. Moreover, there seems to be a step change in behavior: abrasions rates at fill levels above 16% are more or less in line, a low fill level gives much higher abrasion rates.

Powder Surface Velocity and Abrasion

The powder surface velocity has been measured as previously described (10). The powder velocities (v_p) were determined at the conditions described in Table I, and Fig. 3 depicts the results.

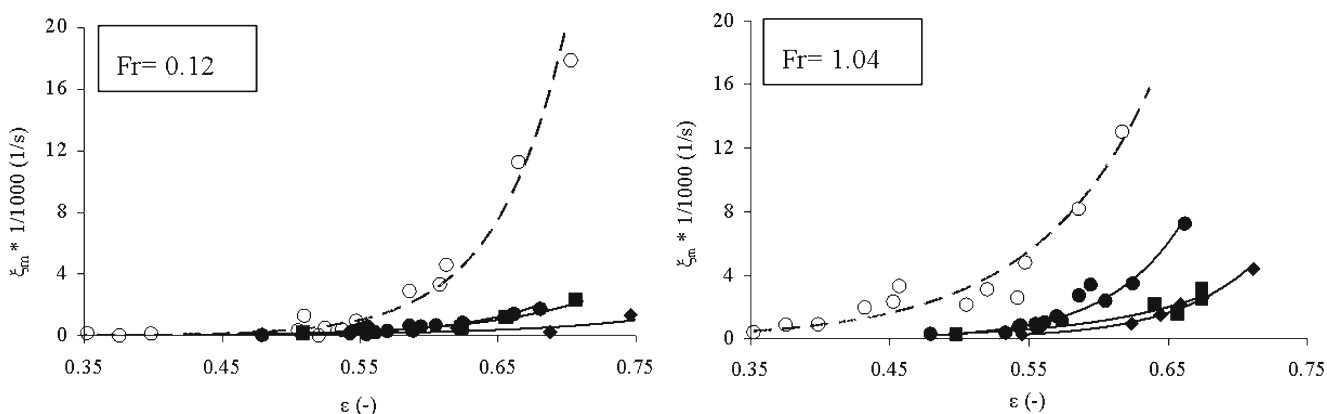


Fig. 2. The mass based abrasion rate constants (ξ_m) of agglomerates for the 25-L high-shear mixer at a ϕ (v/v) of 8% (white circle), 16% (black circle), 27% (black square), and 37% (black diamond)

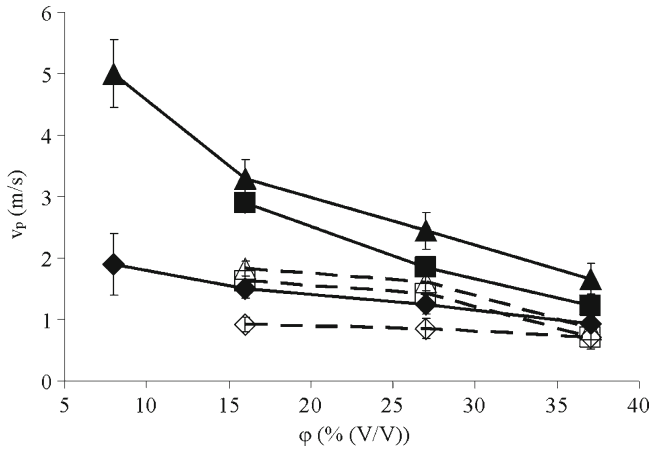


Fig. 3. Powder surface velocities (v_p) at different fill volumes and Froude numbers (black diamond, white diamond: $Fr=0.12$; black square, white square: $Fr=0.46$; black triangle, white triangle: $Fr=1.04$) for the 25-L high-shear mixer (closed symbols and solid lines) and 50-L high-shear mixer (open symbols and dotted lines). Error bars represent the standard deviations (SD) of four subsequent images of two individual experiments

Figure 3 shows decreasing powder surface velocity at increasing relative fill volume. This was observed in both mixers. The figure also shows that the powder velocities measured in the 50-L mixer are significantly lower compared to those in the 25-L mixer scale at comparable Fr numbers. Filler particle velocity is an important parameter in relation to the rate of abrasion of the agglomerates (8,9). The effects were correlated using the Stokes abrasion number (St_{Abr}). Applying St_{Abr} numbers gives the possibility to assess how the abrasion rate constant (ξ_m) scales with process variables in different types/scale of high-shear mixers.

The Stokes abrasion number (St_{Abr}) concept has been discussed in more detail earlier in our previous paper (9). St_{Abr} compares the energy density during blending ($W_b = 0.5 \cdot \rho_b \cdot v_p^2$) with the work of fracture of an agglomerate ($W_f = \frac{\sigma_c^2}{2 \cdot Y}$):

$$St_{Abr} = \frac{\rho_b \cdot v_p^2 \cdot Y}{\sigma_c^2} \quad (3)$$

With ρ_b bulk density of the filler, v_p powder surface velocity, Y elastic moduli, and σ_c fracture stress.

The mechanical properties Y (elastic modulus) and σ_c (fracture stress) of the bCTPs have been calculated as previously described (9) and are based on the porosity (ε) values of the agglomerates. Table II summarizes the fit parameters for elastic moduli and fracture stresses after performing a least square fit analysis assuming exponential relationships (14,15).

Figure 4 shows the relationship between the abrasion rates and the Stokes abrasion numbers in the blending experiments at different working conditions. Visually, three distinct relationships can be seen: with the largest group of tests at fill levels larger than 16% and two groups that both describe relationships when fill level is low.

Model diagnostic plots of the data-set indicate that both variables (ξ_m and St_{Abr}) should be log-transformed before analysis to fulfill the statistical requirements for normal distribution of the values to identify outliers. From these data sets several outlier diagnostics (studentized residuals, DFFITTS,

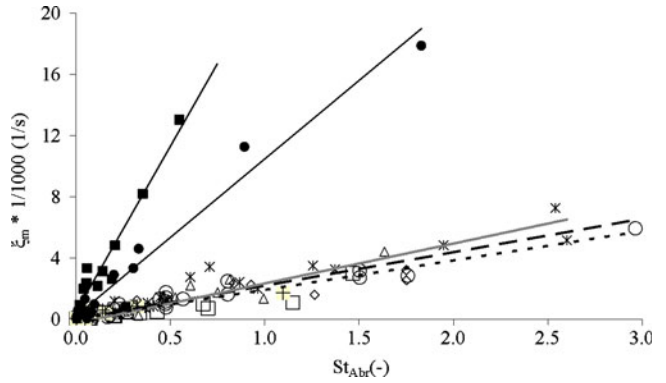


Fig. 4. The relationship between the abrasion rate constants (ξ_m) and the Stokes abrasion number (St_{Abr}) of various bCTPs at defined conditions. The two solid lines indicate the abrasion data deviating from the proposed regression model (dashed line) between ξ_m and St_{Abr} discussed below in the text. The gray and dotted lines indicate the regression model for the 25-L (data-set of $\phi=8\%$ (v/v) excluded) and 50-L mixer scale, respectively. Symbol legend for 50-L mixer scale: white circle: $\phi=16\%$ (v/v) at $Fr=0.12, 0.46, 1.04$; white square: $\phi=27\%$ (v/v) at $Fr=0.12, 0.46, 1.04$; plus sign: $\phi=37\%$ (v/v) at $Fr=0.12, 0.46, 1.04$. Symbol legend for 25-L mixer scale: \times : $\phi=16\%$ (v/v) at $Fr=0.12, 0.46, 1.04$; white diamond: $\phi=27\%$ (v/v) at $Fr=0.12, 0.46, 1.04$; white triangle: $\phi=37\%$ (v/v) at $Fr=0.12, 0.46, 1.04$. Black circle: $\phi=8\%$ (v/v) at $Fr=0.12$; black square: $\phi=8\%$ (v/v) at $Fr=1.04$

leverage, and DFbetas) were used to identify outliers in the data-set of Fig. 4.

From the five curves depicted in Fig. 4, the analyses marked three observations as real outliers. These outliers correspond with bCTPs collected during tests using the 50-L high-shear mixer. This mixer is larger which implicates that larger amounts of filler had to be sieved to collect the model agglomerates. It is likely that this introduces additional errors. This was the rationale to remove the outliers from the data set. These data points are not shown in Fig. 4. After removing these three outliers, different regression models correlating ξ_m and St_{Abr} have been produced:

$$\text{Log}(\xi_m) = \beta + \alpha_i^* \text{Log}(St_{Abr}) \quad (4)$$

Table III lists the models produced.

The results demonstrate a relationship between abrasion rate of agglomerates and the value of St_{Abr} . The R^2 presented in Table III indicates the extent that the values of St_{Abr} explain abrasion at various process conditions. Here, R^2 approaching 100% indicates that abrasion is fully explained by the parameters that describe the Stokes abrasion (St_{Abr}) number of the system. The R^2 presented in Table III shows that the St_{Abr} number is a reasonable way to predict agglomerate abrasion while there is no clear difference between the fits of the results between the different blenders. This makes it possible to combine these results into one model. This model includes 78% of the variance when the fill level exceeds 16%. The regression analysis in our previous study (9) included 84% of the variance using a smaller data set. The data-set in this study also covers the abrasion data for the 50 L high-shear mixer scale.

It is clear that a low fill level leads to much faster abrasion of the test particles (Fig. 4 and Table III). There is apparently a transition where the impeller starts to dominate the abrasion. To study the impact of fill level, regression analysis has been performed separately for all fill levels. These results are depicted in Table IV.

Table III. Regression Models Between ξ_m and St_{Abr} at Various Relative Fill Volumes for the Curves Depicted in Fig. 4

Process condition	Number	Variable	Estimate	95% Confidence limits		R^2 (%)
				Lower	Upper	
$\varphi > 16\%$ (gray line in Fig. 4) (25 L only)	(1)	β	0.78	0.66	0.90	87
		α_i	0.78	0.71	0.85	
$\varphi > 16\%$ (dotted line in Fig. 4) (50 L only)	(2)	β	0.69	0.47	0.90	81
		α_i	0.89	0.77	1.00	
$\varphi > 16\%$ (dashed line in Fig. 4) (25 L and 50 L combined)	(3)	β	0.75	0.63	0.86	78
		α_i	0.83	0.77	0.90	
φ 8% (v/v) at $Fr=0.12$ (solid line)	(4)	β	2.39	1.87	2.92	90
		α_i	1.00	0.84	1.16	
φ 8% (v/v) at $Fr=1.04$ (solid line)	(5)	β	2.76	2.21	3.32	89
		α_i	0.75	0.55	0.96	

To study the effect of the impeller, the fill degree of the blender has been defined relative to the impeller height, the relative fill height (Δh_{powder}):

$$\Delta h_{\text{powder}} = \frac{h_{0,\text{powder}}}{h_{\text{impeller}}} \quad (5)$$

With $h_{0,\text{powder}}$ height of the stationary powder and h_{impeller} the impeller height (Table I). Figure 5 shows the relationship between the fit constants in Table III and the relative fill height of the powder in the blenders.

The slope (α_i) of the fits is almost constant and has a value of around 1. This implicates that the relationships between abrasion rate and St_{Abr} are almost linear relationships. As a consequence, the intercept β describes the slope of the (almost) linear relationships in Fig. 4. The value of β increases drastically when the relative fill height is low.

The intercept between the dotted and solid lines shown in Fig. 5 has been calculated and gives a transition point at a Δh_{powder} value of 3. This result shows that agglomerate abrasion is predominantly determined by the powder bed movements when the Δh_{powder} value is larger than 3. Obviously, the presence of enough powder is a prerequisite for the applicability of the Stokes number approach. When insufficient powder is present, the impeller starts to dominate the process. Logically, direct contact between impeller and the bCTP's yields a deviating abrasive phenomenon than the shear forces occurring when there is plenty of powder present.

Table IV. Regression Models Between ξ_m and St_{Abr} at Various Fill Degree for Two Different High-Shear Mixer Scales Depicted in Fig. 4

Process condition	Number	Variable	Estimate	95% Confidence Limits		R^2 (%)
				Lower	Upper	
16% (v/v) 25 L (Fr=0.12–1.04)	(6)	β	0.93	0.78	1.08	89
		α_i	0.87	0.78	0.96	
27% (v/v) 25 L (Fr=0.12–1.04)	(7)	β	0.62	0.41	0.83	88
		α_i	0.62	0.49	0.75	
37% (v/v) 25 L (Fr=0.12–1.04)	(8)	β	0.65	0.27	1.02	82
		α_i	0.72	0.53	0.92	
16% (v/v) 50 L (Fr=0.12–1.04)	(9)	β	0.77	0.51	1.04	86
		α_i	0.98	0.82	1.15	
27% (v/v) 50 L (Fr=0.12–1.04)	(10)	β	0.63	0.23	1.03	82
		α_i	0.81	0.61	1.02	
37% (v/v) 50 L (Fr=0.12–1.04)	(11)	β	0.67	0.92	0.67	74
		α_i	0.91	0.57	1.26	

CONCLUSION

The abrasion of agglomerates during dry mixing at different fill volumes, impeller rotational speeds, and two different high-shear mixer scales and types has been investigated. This study reveals that the St_{Abr} number is able to predict the

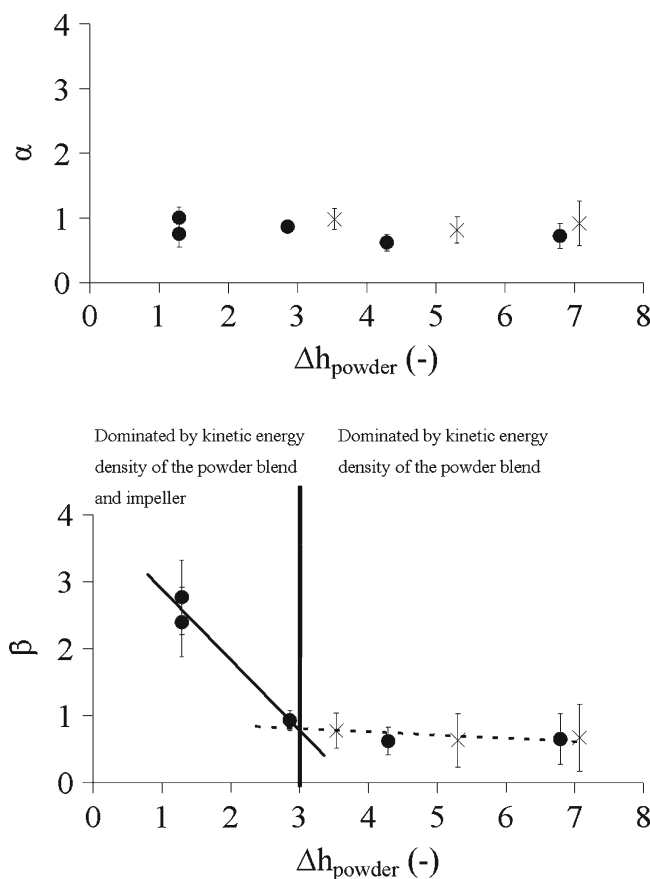


Fig. 5. Relationships between the variables slope (α , upper figure) and intercept (β , lower figure) with the relative distance between impeller and powder height (Δh_{powder}) for the 25 L (black circle) and 50 L (letter x) high-shear mixer scale. The solid horizontal line indicates the transition point between agglomerate abrasion dominated by impeller effects and the kinetic energy density of the powder blend and solely the kinetic energy density of the powder blend. Error bars indicate the $\pm 95\%$ confidence limits

abrasion potential of agglomerates at variable process conditions. This includes high-shear mixers that are geometrically different.

The study reveals a transition point between agglomerate abrasion completely dominated by the powder blend and where a combination of impeller and powder blend effects play a significant role.

The St_{Abr} number concept described in this study demonstrates to be a useful tool to predict the abrasion of agglomerates at conditions during process variation exercises in dry mixing such as transferring the same mixture composition (filler) to a different type and scale of mixer.

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